

**REMARKS**

Entry of the foregoing, reexamination, and further and favorable reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.116, are respectfully requested in light of the remarks which follow.

**I. Claim Amendments**

Claims 1, 3, 5, 10, 24, and 25 are amended herein.

Specifically, several minor amendments have been made to claims 1, 5, 24, and 25, in order to clarify the claim language. These amendments are merely editorial in nature and are not intended to change the scope of the claims or any elements recited therein.

Claim 3 has been amended to depend from claim 2 rather than from claim 1.

Claim 10 has been amended to depend from claim 1 rather than from claim 25.

Finally, new claim 26, reciting the poxviral particle of claim 1 wherein said anti-ligand molecule is differentially expressed or overexpressed in said target cells or is a gene product of a cancer-associated virus, has been added. Claim 26 is supported throughout the specification, for example at page 10, lines 5-8.

The amendments to the claims have been made without prejudice or disclaimer to any subject matter canceled herein. Applicants reserve the right to file one or more continuation and/or divisional applications directed to any canceled subject matter. No new matter has been added, and entry of the foregoing amendments of the above-identified application are respectfully requested.

## **II. Response to Claim Rejections Under 35 U.S.C. § 112**

At pages 2 and 3 of the Office Action, the rejection of claims 1-3, 5, 6, 10-15, 18, 24 and 25 under 35 U.S.C. § 112, first paragraph as purportedly lacking enablement has been maintained for reasons of record.

Specifically, the Examiner has indicated that although the poxvirus particle of the present invention preferentially infects target cells, the particle can also infect non-target cells. The Examiner has concluded that because the specification does not provide guidance as to how the viral particle will spare normal cells, the present claims are not enabled.

Applicants respectfully traverse this rejection for at least the following reasons.

First, the present specification provides a detailed explanation of how the inventive poxviral particles having targeted infection specificity can be constructed. In addition, the working examples describe a poxviral particle having targeted infection specificity towards targeted cells. More specifically, Examples 1 and 2 describe the construction of an MVA poxviral vector which comprises a ligand moiety comprising the scFv chain of the SM3 monoclonal antibody fused to the viral p14 N-terminus. Example 5 provides Western Blot data supporting expression of the ligand moiety SM3 scFv at the surface of the poxviral particles (see page 41 line 27 to page 42 line 8). Importantly, the ligand moiety is accessible for interacting with a MUG-1 peptide, as demonstrated by Surface Plasmon Resonance (see page 42 line 30 to page 43 line 15). Additionally, as explicitly disclosed on page 42, lines 9-29, the infection properties of the SM3 scFv-expressing viral particles (MVATC14552) were assayed on MUC-1-and non-MUG-1-expressing cells (P815 and BHK 21) and

compared to a wild-type MVA vector (MVAN33). Applicants draw the Examiner's attention to Figure 3, which demonstrates that the viral particles having the scFv chain of the SM3 monoclonal antibody exposed at their surface infect MUG-1-expressing cells with a higher efficiency than the P815 and BHK 21 parental cells which do not express MUG-1. In marked contrast, the MVAN33 control infects MUG-1 expressing and non-MUG-1-expressing cells with a similar efficacy.

Second, Applicants note that numerous publications also discuss virus particles having targeted infection specificity, including for instance US 5,543,328; US 5,731,190; US 5,770,442; US 6,576,456; Miller and Vile (1995, FASEB 9, 190-199); Nettelbeck et al. (2001, Molecular Therapy 3(6), 882-891); and Bakker et al. (2001, Gene Ther. 8, 1785-1793). (Copies of the cited scientific publications are enclosed for the Examiner's reference.) As discussed in the cited documents, adenoviruses and retroviruses have been engineered so as to express various ligand moieties specific for an anti-ligand present on targeted cells in order to confer new infection properties towards the targeted cells. The key element for targeting is the exposure of the ligand moiety at the viral surface and its availability for interacting with the anti-ligand molecule located on the target cells. It should be emphasized that the MUG-1-targeted poxviral particle illustrated in the working examples of the current application is capable of expressing the SM3 scFv antibody at the virus surface, of binding its target anti-ligand molecule (*i.e* a MUG-1 peptide), and of preferentially infecting MUG-1 positive cells as compared to cells which do not express MUG-1.

Third, the specification clearly indicates that the "targeted infection specificity" recited in the present claims refers to an enhanced tropism toward the target cells,

as compared to the infection specificity of wildtype poxvirus particles (see, e.g., page 6, lines 1-30). Applicants submit that a person of ordinary skill in the art would have reasonably expected the poxviral particles of the present invention, including those that only preferentially (and not exclusively) infect non-target cells, to be useful for the treatment and/or prevention of clinical conditions. Although delivery systems for gene therapy or cancer treatment, for example, should deliver therapeutic genes or drugs to the appropriate host cells, the stringency with which the therapeutic genes or drugs need to be accurately delivered can vary greatly (see, e.g., page 193 of the review by Miller and Vile).

Bakker et al., for example, demonstrate that an adenoviral vector, modified to target RGD binding integrins, increased the effectiveness of gene therapy for arthritis. Although RGD binding peptides are highly expressed on the target cells (synovium), the tropism of the modified virus was still relatively broad. The authors note that the broad tropism "is not a problem for transfection of the lining cells in the joint, as targeted infection of the synovial lining can be accomplished by the intra-articular injection of the virus" (Miller and Vile, page 1785). In another example, Netterbeck et al. show that adenoviruses with enhanced targeting to vascular cells provide a promising approach in cancer therapy. Notably, the authors used human endoglin (CD105) as a target. CD105 is expressed predominantly, but not exclusively, on the surface of endothelial cells, particularly in angiogenic areas of tumors (Netterbeck et al., page 883). In sum, a person of ordinary skill in the art would not have expected that vector targeting must be refined to the point of absolute specificity in order to be clinically useful.

Thus, Applicants submit that the specification fully enables the poxviral particles recited in the present claims. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

**CONCLUSION**

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.


In the event that there are any questions relating to this Amendment and Reply, or the application in general, it would be appreciated if the Examiner would telephone the undersigned attorney at 703-838-6609 concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

BUCHANAN INGERSOLL PC

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By:



Lisa E. Stahl

Registration No. 56,704

P.O. Box 1404  
Alexandria, VA 22313-1404  
703.836.6620